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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/763,308	02/20/2001	Per-Ola Arvidsson	06275-228001	5091

26161 7590 01/27/2005

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EXAMINER	
EPPERSON, JON D	
ART UNIT	**PAPER NUMBER**
1639	

DATE MAILED: 01/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/763,308	ARVIDSSON ET AL.	
	Examiner	Art Unit	
	Jon D Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 6-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 6-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination (RCE)

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/28/04 has been entered. Claims 1-14 were pending. Applicants canceled claims 4, 5 and 12-14. In addition, Applicants amended claim 1. No new claims were added. Therefore, claims 1-3 and 6-11 are currently pending and active in the instant application. An action on the merit follows.

Those sections of Title 35, US code, not included in the instant action can be found in previous office actions.

Withdrawn Objections/Rejections

2. The Enablement rejection under 35 U.S.C. 112, first paragraph is withdrawn in view of Applicants' arguments and/or amendments. All other rejections are maintained and the arguments are addressed below.

Outstanding Rejections

Claims Rejections - 35 U.S.C. 102

3. Claims 1-3 and 6-11 are rejected under 35 U.S.C. 102(a) as being anticipated by Henco et al. (EP 0 947 820 A2) (Date of Publication is **October 6, 1999**).

For ***claims 1-3, 6-11***, Henco et al. (see entire document) disclose the use of cyclodextrins (including Applicant's elected 2-hydroxypropyl-β-cyclodextrin, see claim 7) as additives for compound storage including pharmaceutical compounds of molecular weight <1000 Daltons (e.g., see page 3, paragraph 17, "The present invention has applications in high throughput screening (HTS) for pharmaceutically active compounds requiring efficient release/dissolution of intact ingredients in the presence of assay buffer"), which anticipates claims 1-11. Please note that the additive is first combined to a solution of the compounds and thus is also prepared (at least for a while) in a wet form. Furthermore, Henco et al. disclose 4-10% by weight that falls within applicants' claimed specification range of 30-150 or 40-80 or 45-60 or 50 mM values (e.g., see Henco, claim 8; see especially page 2, paragraph 7, line 43; see also page 4 of Applicants' specification for conversion chart from % wt to mM concentration). Furthermore, Henco et al. disclose that the cyclodextrin can be applied to libraries that contain hundreds of thousands of compounds like the ones typically used in high throughput screening (e.g., see page 2, line 6; see also page 3, line 39; see also page 4, line 9; see also figures).

Response

4. Applicant's arguments directed to the above 35 U.S.C. § 102 rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Applicants argue that Henco should not be considered prior art because Applicants foreign priority date (i.e., August 24, 1999) is before the publication date of Henco (i.e., October 6, 1999). Furthermore, Applicants state that they "... will submit a certified copy of the foreign priority application in the near future." (e.g., see 10/28/04 Response, page 6, §102 Rejection section).

This is not found persuasive for the following reasons:

The Examiner contends that Henco is prior art because Applicants priority foreign priority request has not been granted. Applicants have not sent a certified copy to the USPTO (e.g., see MPEP § 201.15). Therefore, Applicants arguments are moot.

Accordingly, the 35 U.S.C. § 102(a) rejection cited above is hereby maintained.

Claim Rejections - 35 USC § 103

5. Claims 1-3, 6-9 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Szente et al. (Szente, L.; Harangi, J.; Szejtli, J. "Long term storage stability studies on flavour β-cyclodextrin complexes" Proc. Int. Symp. Cyclodextrins, 4th (1988), 545-9. Editor(s): Huber, O.; Szejtli, J. Kluwer: Dordrecht, Neth.) and Tabushi et al. (Tabushi, I.; Yamamura, K.; Fujita, K.; Kawakubo, H. "Specific Inclusion Catalysis by β-Cyclodextrin in the One-Step Preparation of Vitamin K1 or K2 Analogues" *J. Am. Chem. Soc.* **1979**, *101(4)*, 1019-1026) and Applicants' admission in the Specification.

For ***claims 1***, Szente et al. (see entire document) disclose adding β-cyclodextrin to a library of natural and synthetic flavors to prevent degradation for periods as long as 10

years (see Szente et al., Summary), which reads on claim 1. Although Szente et al. do not explicitly state that they are adding cyclodextrin to a library with "at least 100 compounds", each of the 21 "flavors" listed in Table 1 contains ~10-20 compounds (e.g., see figures 1 and 2 wherein for (1) Garlic and (2) Dill "flavors" contain approximately ~32 compounds exemplified by the ~19 and ~13 large and small peaks shown in the chromatographs, respectively) and, as a result, a library of approximately 21 × ~10-20 compounds is generated (i.e., a library of approximately 200 to 400 compounds). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.). Thus, the flavors listed in Table I inherently contain >100 compounds and, in addition, more "flavors" and thus more compounds would be immediately envisioned by a person of skill in the art. Furthermore, Szente et al. disclose storing each of said compounds in cyclodextrin for periods as long as 10 years (e.g., see Szente et al., Table 1).

For ***claim 11***, Szente et al. disclose storing in "normal humidity" which reads on a "wet form" (e.g., see Szente et al., Experimental Section).

The prior art teaching of Tabushi et al. differ from the claimed invention as follows:

For ***claim 1, 6-9***, the prior art teachings of Szente et al. do not specifically recite the use of 20-200mM concentration of cyclodextrin. The reference is silent on this issue (i.e., no cyclodextrin concentration is given).

For ***claims 2-3***, the prior art teachings of Szente et al. differ from the claimed invention by not specifically reciting the use of a library comprising at least 1000 or 10000 members.

However, Specification teach the following limitations that are deficient in Tabushi et al.:

For ***claims 1, 6-9 and 11***, Tabushi et al. (see entire document) disclose adding β-cyclodextrin to a library of Vitamin K analogues to prevent them from H_2O_2 attack (e.g., see Tabushi et al., page 1023, scheme I showing protection of compound(s) **18** from H_2O_2 attack; see also page 1020, column 2, compounds 7 and 8 wherein the R groups are defined; please note that the Vitamin K analogs are less than 1000 Da). Furthermore, Tabushi et al. disclose using a 50mM concentration of β-cyclodextrin and also disclose varying the concentration of β-cyclodextrin in relation to the compounds in the library and, as a result, would anticipate any other concentration as well (e.g., see Tabushi et al., page 1020, Table 1, superscript "a" denoting the β-cyclodextrin concentration at "5×10^{-2} M"; see also column 2, paragraph 1).

For ***claims 2-3***, the Specification teach that compound libraries may contain more than 100,000 different compounds and can be used in high throughput screening (e.g., see Specification, paragraph 2-3; see especially paragraph 2, lines 10-11, "Compound libraries may for example contain more than 100,000 different compounds").

It would have been obvious to one skilled in the art at the time the invention was made to use the 50 mM concentration of cyclodextrin as taught by Tabushi et al. for the storage of the natural and synthetic flavor compounds as taught by Szente et al. because both references use cyclodextrin to protect compound libraries (i.e., the references represent analogous art). Furthermore, a person of ordinary skill would have been motivated to combine the references because Tabushi et al. teach that phenolic compounds can be protected using cyclodextrin at 50 mM concentration, which would extend to the phenolic compounds disclosed by Szente et al. (e.g., see Tabushi et al., scheme I outlining mechanism for protecting phenolic compounds; see also Szente et al. wherein phenolic compounds are disclosed).

In addition, it would be conventional and within the skill of the art to *identify the optimal concentration*. It is well-established that merely selecting proportions and ranges is not patentable absent a showing of criticality. In re Becket, 33 U.S.P.Q. 33 (C.C.P.A. 1937). In re Russell, 439 F. 2d 1228, 169 U.S.P.Q. 426 (C.C.P.A. 1971). See also MPEP 2144.05 II.A., "Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. '[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.' In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40C and 80C and an acid concentration between 25 and 70% was held to be prima facie

obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100C and an acid concentration of 10%.).

In addition, it would have been obvious to screen larger libraries than the ones taught by Szente et al. and Tabushi et al. (i.e., libraries with more than 100,000 compounds) with the β-cyclodextrins because the Specification admits that larger libraries can be used for screening purposes which would include the biological (e.g., test screening) and/or pharmaceutical screening set forth by the Szente et al. and Tabushi et al. references. Furthermore, one of ordinary skill in the art would have been motivated to use β-cyclodextrins with larger libraries of susceptible phenolic compounds to protect more compounds from potential H_2O_2 attack and/or other forms of degradation before screening.

Response

6. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue, "Szente does not disclose a cyclodextrin concentration of 20-200 mM as required by the pending claims" (e.g., see 10/28/04 Response, paragraph bridging pages 7-8).

[2] Applicants argue, "... one skilled in the art would not have been motivated to modify Szente's concentrations to provide the concentrations required by the pending claims" (e.g., see

10/28/04 Response, page 7, paragraph 1; see also page 7, paragraph 4 where the argument is repeated).

[3] Applicants argue, "even [if] one skilled in the art were somehow motivation to modify Szente's cyclodextrin concentration, consideration would not have been given to Tabushi because Tabushi is directed to an entirely different use of cyclodextrins from Szente" (e.g., see 10/28/04 Response, page 7, paragraph 2).

[4] Applicants argue, "... to the extent that Applicants' specification is available as prior art, Applicants' specification does not cure the infirmities of Szente and Tabushi ... [because it] does not disclose or suggest compound libraries where each compound is stored in the presence of a cyclodextrin having a concentration of 20-200 mM" (e.g., see Tabushi et al. page 7, paragraph 3).

This is not found persuasive for the following reasons:

[1] In response to applicants' arguments against the Szente reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

[2] In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir.

1992). Here, a person of ordinary skill would have been motivated to combine the references because Tabushi et al. teach that phenolic compounds can be protected using cyclodextrin at 50 mM concentration, which would extend to the phenolic compounds disclosed by Szente et al. (e.g., see Tabushi et al., scheme I outlining mechanism for protecting phenolic compounds; see also Szente et al. wherein phenolic compounds are disclosed). Please note that "there is no requirement that the prior art provide the same reason as the applicant to make the claimed invention", see MPEP § 2144").

In addition, Applicant's arguments fail to comply with 37 CFR 1.111(b) because they amount to a general allegation that the claims define a patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the references. In this case, Applicants state that there is no motivation to combine, but they do not provide a reason and/or evidence to support this accusation.

[3] The Examiner respectfully disagrees. Both references use "cyclodextrin" and, as a result, the references represent analogous art. In addition, both references teach how to protect phenolic compounds from degradation (e.g., see Tabushi et al., scheme I outlining mechanism for protecting phenolic compounds; see also Szente et al. wherein phenolic compounds are disclosed). Therefore, Applicants' statements to the contrary are completely unsupported.

[4] In response to applicants' arguments against the specification being used as a reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

7. Claims 1-3, 6-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Szente et al. (Szente, L.; Harangi, J.; Szejtli, J. "Long term storage stability studies on flavour β-cyclodextrin complexes" Proc. Int. Symp. Cyclodextrins, 4th (1988), 545-9. Editor(s): Huber, O.; Szejtli, J. Kluwer: Dordrecht, Neth.) and Tabushi et al. (Tabushi, I.; Yamamura, K.; Fujita, K.; Kawakubo, H. "Specific Inclusion Catalysis by β-Cyclodextrin in the One-Step Preparation of Vitamin K1 or K2 Analogues" *J. Am. Chem. Soc.* **1979**, *101(4)*, 1019-1026) and Castillo et al. (U.S. Patent No. 5,985,310) (102(e) Date is ***March 10, 1998***) and Applicants' admission in the specification.

For ***claims 1-3, 6-9 and 11***, the combined teachings of Szente et al., Tabushi et al., and the specification render obvious claims 1-3, 6-9 and 11 (see 35 U.S.C. 103(a) rejection above, which is incorporated in its entirety herein by reference).

The combined prior art teaching of Szente et al., Tabushi et al. and the specification differ from the claimed invention as follows:

For ***claim 10***, the combined prior art teachings of Szente et al., Tabushi et al., and the specification differ from the claimed invention by not specifically reciting the use of a 2-hydroxypropyl-β-cyclodextrin. The combined teachings only recite β-cyclodextrin (e.g., see Tabushi et al., page 1020, Table 1, superscript "a" denoting the β-cyclodextrin concentration at "5×10^{-2} M"; see also column 2, paragraph 1).

However, Castillo et al. teach the following limitations that are deficient in Tabushi et al.:

For ***claim 10***, Castillo et al. (see entire document) teach 2-hydroxypropyl-β-cyclodextrin can be used with pharmaceutical formulations (see column 1, lines 27-35).

It would have been obvious to one skilled in the art at the time the invention to use 2-hydroxypropyl-β-cyclodextrin as taught by Castillo in place of β-cyclodextrin as taught by the combined references of Szente et al., Tabushi et al. and the specification because Castillo et al. disclose that the 2-hydroxypropyl-β-cyclodextrin is useful in pharmaceutical preparations, which would encompass the phenolic libraries disclosed by Tabushi et al. and Szente et al. and because the structures of β-cyclodextrin and 2-hydroxypropyl-β-cyclodextrin are structurally related (i.e., the references represent analogous art) and thus would be expected to have similar beneficial properties. Furthermore, one of ordinary skill in the art would have been motivated to use 2-hydroxypropyl-β-cyclodextrin with the libraries disclosed by Szente et al. and Tabushi et al. because Castillo et al. explicitly state that they are good replacements for β-cyclodextrin (see Castillo et al., column 1, lines 27-35, "There have been a number of attempts to derivative cyclodextrins in order to decrease toxicity or increase solubility. For example, hydroxy-propyl-β-cyclodextrin is a derivative which has been shown to have a relatively low toxicity and a high aqueous solubility as compared to the parent compound, β-cyclodextrin") (emphasis added).

Response

8. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue, "The combination of Szente, Tabushi and Applicants' specification is disclosed above where it is demonstrated that this combination of references does not render the pending claims obvious" (e.g., see 10/28/04 Response, page 7, last paragraph).

[2] Applicants argue, "In addition, one skilled in the art would not have been motivated to combine Tabushi and Castillo because, whereas Tabushi discloses the use of cyclodextrins as a reaction catalyst for particular compounds relating to vitamin K (see Tabushi at Summary), Castillo is interested in finding a preservative that works in the presence of cyclodextrin" (e.g., see 10/28/04 Response, page 8).

This is not found persuasive for the following reasons:

[1] To the extent that Applicants' arguments directed to the above 35 U.S.C. § 103 rejection are repeated here, the Examiner contends that those arguments have been adequately addressed in that section, which is incorporated in its entirety herein by reference.

[2] In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the

knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, it would have been obvious to one skilled in the art at the time the invention to use 2-hydroxypropyl-β-cyclodextrin as taught by Castillo in place of β-cyclodextrin as taught by the combined references of Szente et al., Tabushi et al. and the specification because Castillo et al. disclose that the 2-hydroxypropyl-β-cyclodextrin is useful in pharmaceutical preparations, which would encompass the phenolic libraries disclosed by Tabushi et al. and Szente et al. and because the structures of β-cyclodextrin and 2-hydroxypropyl-β-cyclodextrin are structurally related and thus would be expected to have similar beneficial properties. Thus, contrary to the assertion made by Applicants, the references do represent analogous art. Furthermore, one of ordinary skill in the art would have been motivated to use 2-hydroxypropyl-β-cyclodextrin with the libraries disclosed by Szente et al. and Tabushi et al. because Castillo et al. explicitly state that they are good replacements for β-cyclodextrin (see Castillo et al., column 1, lines 27-35, "There have been a number of attempts to derivative cyclodextrins in order to decrease toxicity or increase solubility. For example, hydroxy-propyl-β-cyclodextrin is a derivative which has been shown to have a relatively low toxicity and a high aqueous solubility as compared to the parent compound, β-cyclodextrin"). Thus, adequate motivation is provided and all of the limitations are addressed as outlined in the rejection above.

New Rejections

Claims Rejections - 35 U.S.C. 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Robinson et al. (Robinson, G. M.; Taylor, E. W.; Smyth, M. R.; Lunte, C. E. "Application of capillary electrophoresis to the separation of structurally diverse N-(substituted)-glycine-peptoid combinatorial mixtures" *Journal of Chromatography B* **1998**, *705*, 341-350) as evidenced by Zuckermann et al. (Zuckermann, R. N.; Martin, E. J.; Spellmeyer, D. C.; Stauber, G. B.; Shoemaker, K. R.; Kerr, J. M.; Figliozzi, G. M.; Goff, D. A.; Siani, M. A.; Simon, R. J.; Banville, S. C.; Brown, E. G.; Wang, L.; Richter, L. S.; Moos, W. H. "Discovery of Nanomolar Ligands for 7-Transmembrane G-Protein-Coupled Receptors from a Diverse N-(Substituted)glycine Peptoid Library" *J. Med. Chem.* **1994**, *37*, 2678-2685) and as evidenced by Erra-Balsells et al. (Erra-Balsells, R.; Nonami, H. "UV-Matrix-assisted Laser Desorption/Ionization Time-of-flight Mass Spectrometry Analysis of Synthetic Polymers by using nor-Harmane as Matrix" ARKIVOC **2003**, (x), 517-537). Please note: MPEP 2131.01(d) permits the citation of references or evidence in an anticipation rejection under 35 U.S.C. § 102 in order to show that a characteristic not disclosed in the reference is inherent.

For ***claim 1***, Robinson et al. disclose a compound library comprising at least 100 compounds (e.g., see Table 1 wherein a library of NSG-peptoids is disclosed composed of 5 "CHIR" variants x 24 "side chain" groups = 120 library members; see also page 342, column 1, paragraph 1). In addition, Robinson et al. disclose that said compounds are have molecular weights less than 1000 Daltons (e.g., see Table 1 wherein M_w are disclosed for each of the 5 CHIR variant mixtures). Robinson et al. do not explicitly state that their N-(substituted)-glycine-peptoid library represents a library of "pharmaceutical" compounds (e.g., Robinson et al., page 341, column 1, paragraph 1 wherein Robinson et al. imply pharmaceutical use, "The development of this method was based on the use of a particular N-(substituted)-glycine (NSG)-peptoid mixture, CHIR 4580, as a representative of mixtures which may be encountered during drug discovery"). However, Zuckermann et al. explicitly disclose that N-(substituted)glycine peptoid libraries bind with nanomolar affinity to 7-transmembrane G-Protein Coupled receptors such as the α_1-adrenergic receptor and the μ-opiate receptor (e.g., see Zuckermann et al., title and abstract). Thus, the N-(substituted)-glycine (NSG)-peptoid library disclosed by Robinson et al. must inherently possess the same pharmaceutical properties (e.g., ability to bind to 7-transmembrane G-protein coupled receptors). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923

(PTO Bd. Pat. App. & Int.). Finally, Robinson et al. disclose that each member of the library is stored in the presence of a cyclodextrin wherein said cyclodextrin concentration is, for example, 26 mM (e.g., see figures 2, 3, 4, 6 and 8 wherein methyl-β-cyclodextrin was added to the library members at, for example, 40 mg/ml, which corresponds to 26 mM using the 1500 m.w. value for methyl-β-cyclodextrin as disclosed by Erra-Balsells et al. on page 532, Experimental Section i.e., the molecular weight of methyl-β-cyclodextrin is an inherent property of the molecule).

For ***claim 11***, Robinson et al. disclose the library in a "wet" form (e.g., see figures 2, 3, 4, 6 and 8 wherein the libraries are in aqueous solution).

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 1-3 and 6-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Robinson et al. (Robinson, G. M.; Taylor, E. W.; Smyth, M. R.; Lunte, C. E. "Application of capillary electrophoresis to the separation of structurally diverse N-(substituted)-glycine-peptoid combinatorial mixtures" *Journal of Chromatography B* **1998**, *705*, 341-350) and Zuckermann et al. (Zuckermann, R. N.; Martin, E. J.; Spellmeyer, D. C.; Stauber, G. B.; Shoemaker, K. R.; Kerr, J. M.; Figliozzi, G. M.; Goff, D. A.; Siani, M. A.; Simon, R. J.; Banville, S. C.; Brown, E. G.; Wang, L.; Richter, L. S.; Moos, W. H. "Discovery of Nanomolar Ligands for 7-Transmembrane G-Protein-Coupled Receptors from a Diverse N-(Substituted)glycine Peptoid Library" *J. Med. Chem.* **1994**, *37*, 2678-2685) and Applicants' admission in the Specification and Rajewski et al. (Rajewski, R. A.; Stella, V. J. "Pharmaceutical Applications of Cyclodextrins. 2. In vivo Drug Delivery" Journal of Pharmaceutical Sciences 1996, 85, 11, 1142-1169) as evidenced by Erra-Balsells et al. (Erra-Balsells, R.; Nonami, H. "UV-Matrix-assisted Laser Desorption/Ionization Time-of-flight Mass Spectrometry Analysis of Synthetic Polymers by using nor-Harmane as Matrix" ARKIVOC **2003**, (x), 517-537).

For ***claims 1 and 11***, Robinson et al. teach all the limitations stated in the 35 U.S.C. 102(b) rejection above (incorporated in its entirety herein by reference), which anticipates and, as a result, renders obvious claims 1 and 11.

The prior art teaching of Robinson et al. differ from the claimed invention as follows:

For ***claims 2-3***, the prior art teachings of Robinson et al. differ from the claimed invention by not specifically reciting the use of a library with at least 1000 compounds or 10,000 compounds. Robinson et al. only teach the use of 120 compounds (e.g., see Table 1 wherein a library of NSG-peptoids is disclosed composed of 5 "CHIR" variants × 24 "side chain" groups = 120 library members; see also page 342, column 1, paragraph 1).

For ***claims 6-9***, the prior art teachings of Robinson et al. do not specifically recite, for example, the use of 50 mM concentration of cyclodextrin. The reference only recites 26 mM cyclodextrin concentration (e.g., see figures 2, 3, 4, 6 and 8 wherein methyl-β-cyclodextrin was added to the library members at, for example, 40 mg/ml, which corresponds to 26 mM using the 1500 m.w. value for methyl-β-cyclodextrin as disclosed by Erra-Balsells et al. on page 532, Experimental Section i.e., the molecular weight of methyl-β-cyclodextrin is an inherent property of the molecule).

For ***claim 10***, the prior art teachings of Robinson et al. fail to recite the use of 2-hydroxypropyl-β-cyclodextrin. Robinson et al. only teach the use of methyl-β-cyclodextrin.

However, Zuckermann et al. and the admission in Applicants' specification teach the following limitations that are deficient in Robinson et al.:

For ***claims 2-3***, the combined teachings of Zuckermann et al. (see entire document) and the admission in Applicants' specification teach the use of larger libraries including a 5,000 member NSG library (e.g., see Zuckermann et al., abstract) and Applicants' specification teach that compound libraries may contain more than 100,000 different compounds for use in high throughput screening (e.g., see Specification,

paragraph 2-3; see especially paragraph 2, lines 10-11, "Compound libraries may for example contain more than 100,000 different compounds").

For ***claims 6-9***, Rajewski et al. disclose (see entire document) the use of 50 mM cyclodextrin and also that adjusting said concentration was well within the capabilities of a person of skill in the art to adjust the solubility of a drug to which the cyclodextrin interacts (e.g., see Rajewski et al., figure 2).

For ***claim 10***, the prior art teachings of Rajewski et al. disclose the use of hydroxypropyl-β-cyclodextrin (e.g., see page 1143, column 2, paragraph 2; see also page 1144, column 2, second to last paragraph, "Because of the solubility limits and the safety concerns CD, numerous chemical modifications of the cyclodextrins have been made ... The cyclodextrins of prime interest to pharmaceutical scientists consist of the hydroxypropyl and hydroxyethyl cyclodextrins ... especially 2-hydroxypropyl").

It is well established that merely selecting proportions and ranges is not patentable absent a showing of criticality. In re Becket, 33 U.S.P.Q. 33 (C.C.P.A. 1937). In re Russell, 439 F. 2d 1228, 169 U.S.P.Q. 426 (C.C.P.A. 1971). See also MPEP 2144.05 II.A., "Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. '[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.' In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40C and 80C and an acid concentration between 25 and 70% was held to be prima facie

obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100C and an acid concentration of 10%.). Here, Applicants are merely trying to establish an "optimum range" for the "concentration" of cyclodextrin, which clearly falls within the scope of routine experimentation as exemplified by Rajewski et al. (e.g., see Rajewski et al., page 1144. figure 2 demonstrating that cyclodextrin concentration was routinely "adjusted" for any drug to maximize and/or adjust the drug's solubility; Rajewski et al. further disclose that a very simple "linear" relationship exists for many pharmaceuticals that form a 1:1 complex with the cyclodextrin as shown in figure 2A). Thus, adjusting the 26 mM concentration disclosed by Robinson et al. to Applicants' claimed scope of 30, 40 or even 50 mM clearly represents routine experimentation by one of ordinary skill in the art in accordance with MPEP 2144.05 II.A. Furthermore, Applicants have not provided any showing of "criticality" that would overcome this presumption.

In addition, it would have been obvious to substitute the 2-hydroxypropyl cyclodextrin as disclosed by Rajewski et al. for the methyl-β-cyclodextrin as disclosed by Robinson et al. because Rajewski et al. state that that many cyclodextrins can be used interchangeably, for example, Rajewski et al. disclose that both methyl-β-cyclodextrin and 2-hydroxypropyl were developed as replacements for cyclodextrin (e.g., see Rajewski et al., page 1144, column 2, second to last paragraph). Furthermore, a person of skill in the art would have been motivated to use the 2-hydroxypropyl derivative because of its favorable properties with regard to solubility and safety (e.g., see Rajewski et al., page 1143, column 2, paragraph 2; see also page 1144, column 2, second to last

paragraph, "Because of the solubility limits and the safety concerns CD, numerous chemical modifications of the cyclodextrins have been made ... The cyclodextrins of prime interest to pharmaceutical scientists consist of the hydroxypropyl and hydroxyethyl cyclodextrins ... especially 2-hydroxypropyl"). Finally, a person of skill in the art would have had a reasonable expectation of being successful because methyl-β-cyclodextrin and 2-hydroxypropyl cyclodextrin represent functional equivalents with very similar structures (see above).

It would also have been obvious to analyze the NSG-peptoid libraries disclosed by Zuckermann using the CE technique disclosed by Robinson et al. because Robinson et al. explicitly state that their CE technique can be used for this purpose i.e., to analyze NSG-peptoid libraries (e.g., see Robinson et al., Title and Abstract). Furthermore, a person of skill in the art would have been motivated to use the libraries of Zuckermann et al. because Robinson et al. state that their purpose is to analyze mixtures that "might be encountered during drug discovery" and disclose NSG-peptoid libraries as a "preferred embodiment" (e.g., see Robinson et al., page 341, column 1, paragraph 1; see also page 349, Conclusion section; see also abstract), which would encompass the pharmaceutically active NSG-peptoids disclosed by Zuckerman (e.g., see Zuckerman et al., abstract wherein binding to G-protein-coupled receptors is disclosed). Finally, a person of skill in the at would have reasonably expected to be successful because Robinson et al. demonstrate their CE technique on a library of structurally related compounds (e.g., see Robinson et al., page 350, column 1, first full paragraph, "In this report the separation of a variety of NSG-peptoid mixtures ... using modified CE BGEs was demonstrated";

compare also the structures shown in figure 1 of Robinson et al. to the structures shown in Figures 3 and 4 of Zuckermann et al.) and further state that their method "... provided sufficient separation of [NSG-peptoid] mixtures ...[that] exhibited a wide range of physical and chemical properties and for physicochemically different mixtures. In addition, if further resolution is required for a particular mixture, the methods are readily modified in a relatively predictable manner to achieve the desired separation ... [and that their method] provides an extremely powerful separation technique for [NSG-peptoid] combinatorial mixtures", which would encompass the NSG-peptoid combinatorial mixtures disclosed by Zuckermann et al.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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January 14, 2005